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ScienceDirect
British Journal of Oral and Maxillofacial Surgery 50 (2012) 321–327
BRITISH Journal of Oral and Maxillofacial Surgery
www.bjoms.com

Randomised controlled feasibility trial on the use of medical grade honey following microvascular free tissue transfer to reduce the incidence of wound infection

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Accepted 17 July 2011
Available online 9 August 2011

Abstract

The aim of this study was to assess the feasibility of using Leptospermum honey in a randomised trial to reduce the incidence of wound infection after microvascular free tissue reconstruction for cancer of the head and neck. During the one-year study period 70 consecutive patients were admitted to the regional maxillofacial ward for free tissue reconstruction. Of these, 56 (80%) consented to be randomised and 49 (70%) were actually randomised, 25 into the honey dressings group, and 24 into the conventional dressings group (control). Six patients were missed when consent was required, 8 did not consent, and 7 who had given consent were missed at the randomisation stage in theatre. Results of wound swabs were positive in 36% of the honey group and 38% of the control group. Methicillin-resistant *Staphylococcus aureus* (MRSA) was found in 28% and 25%, respectively. Of these, 38% were deemed to require intervention. Honey dressings were acceptable to both patients and nurses. There was a reduction ($p < 0.05$) in duration of hospital stay in the honey group (median 12 days, IQR 10–21) compared with the control (median 18 days, IQR 13–28). The cost of standard and honey dressings was similar. This feasibility study has shown that a randomised controlled trial (RCT) is possible and that several hundreds of patients would be required to show a clinical benefit for honey. Further research is needed to confirm a shorter duration of hospital admission and if so, whether this is due to more rapid healing.

Keywords: Wound infection; MRSA; Reconstructive surgery; Head and neck cancer, Randomised control trial

Introduction

Postoperative wound infections are associated with increased morbidity,[1,2] additional surgery, increased duration of hospital stay, higher cost of treatment, and prolonged periods of wound dressing.[3] They also have a detrimental impact on the psychological well-being of patients. [4,5] Patients with head and neck cancer are perhaps more susceptible to infection given their age, comorbidities, extensive operations, and the potential for multiple wound sites such as tracheostomy,

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doi:10.1016/j.bjoms.2011.07.014

neck dissection, and pedical or free tissue donor sites. There are several notable pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), haemolytic streptococci, methicillin-sensitive *S. aureus* (MSSA), and *Pseudomonas aeruginosa*, of which MRSA is of most interest to this study.

MRSA infection in patients with head neck cancer has been well-reported in different countries (UK, France, Ireland, Japan) in small case series,[6–8] retrospective audits,[9–12] and audits of changes in antibiotic policy.[13] Infection rates vary from 14%[12] to 45%.[10] In the UK there have been several government and local initiatives to reduce infection on hospital wards including MRSA screening before admission, "bare below the elbow", and "clean your hands" campaigns, the availability of side rooms, and guidelines to restrict the use of antibiotics.

Honey consists of a concentrated solution of sugars with low water content that restricts microbial growth.[14] Some honeys contain a currently unidentified plant-derived compound with antimicrobial activity, and they have anti-inflammatory properties and help to heal wounds quickly by stimulating tissue regeneration.[14] Jull et al.[15] published a systematic review of honey as a topical treatment for wounds, which included 19 trials and over 2500 participants. In a systematic review of the use of honey and its potential value in oncology care, Bardy et al.[16] investigated whether it has a role in healthcare, its applicability to cancer care, and made recommendations for practice. A total of 43 studies including RCTs, comparative studies, case studies, and systematic reviews, were examined.

There is a paucity of studies that specifically report the use of honey in patients with head and neck cancer. Visavadia et al.[17] published a short communication about two patients with chronic wounds infected by MRSA: one had a split skin graft (SSG) that had failed to heal for four months, and the other had an infected radial forearm flap donor site. Both were treated with honey and they healed at two and five weeks, respectively. Currently we know of no published studies on the prophylactic use of honey dressings to prevent wound infections after operations of any type. However, Johnson et al.[18] compared the application of Medihoney™ (Medihoney (Europe) Ltd) three times a week with mupirocin for the prevention of catheter-associated infections in patients on haemodialysis and found no significant difference. They concluded that the use of honey was safe, inexpensive, and effective compared with 2% calcium mupirocin.

In a head and neck setting it was not clear how acceptable wound dressings with honey would be to patients and nursing staff. Although there is a theoretical basis to support the use of honey there are no data upon which to base a design for a definitive randomised trial to test its efficacy, so we aimed to assess the feasibility of using Leptospermum honey in a randomised controlled trial (RCT) to reduce the incidence of wound infection after microvascular free tissue reconstruction for cancer of the head and neck. Aspects of feasibility included recruitment and drop-out rates, acceptability of honey to patients and nursing staff, the appropriateness of the timing and sites of wound swabs, appropriateness of methods of data collection, and a calculation of appropriate sample size for future study.

Method

Patients

Eligible patients required microvascular free tissue reconstruction at the regional maxillofacial unit, and recruitment was for 12 months from February 2008. Those who had had previous operations for head and neck cancer or reconstruction, previous infection with MRSA, previous radiotherapy, or serious comorbidities (for example, diabetes) were not excluded. Exclusions comprised a history of neuroses, psychoses or dementia, a known allergy to honey products, or those already recruited for another trial (patients having extra nutritional feed by percutaneous endoscopic gastrostomy (PEG)). The medical statistician prepared randomised envelopes in advance using simple blocked randomisation. They were opened in sequential order by the surgeon when the patient was in theatre.

Dressings

Patients in the honey arm had sterilised medical-grade antibacterial honey applied to their wounds (neck, donor site, free flap) while those in the control arm had conventional dressings applied. There was no suitable placebo for honey; the trial was neither double nor single blind. Wound dressings and honey were applied in theatre after operation. Free flap donor sites were left undisturbed for 7–10 days. Honey was applied to suture lines daily, and after 10 days was applied to the free flap wound. In the conventional arm the suture lines were left exposed. For wounds that deteriorated a clinical decision was made by the tissue viability team about whether it was appropriate to continue using conventional dressings or honey.

The honey used was Medihoney™ Antibacterial Wound Gel™, a blend of gamma irradiated Australian and New Zealand honey from Leptospermum sp (jelly bush and manuka, respectively) mixed with natural waxes to thicken it for ease of application.

Swabbing of wounds

Baseline swabs were taken either at the preoperative clinic or on admission the day before operation. All wounds, suture lines, tracheostomy sites, nose, and groin were swabbed 7 days after operation. Free flaps, split skin sites, or full thickness grafts were swabbed on removal of the theatre dressing at 7 or 10 days and again at discharge, or at 28 days if still in hospital. Nose, groin, and wound swabs were cultured for MRSA, haemolytic streptococci, (MSSA), *Ps. aeruginosa*, and other serious wound pathogens in accordance with

standard laboratory operating procedures. All strains of MRSA were saved. Swabs were taken whenever patients showed signs of infection between programmed swabs. Follow-up of patients ended after 28 days. Laboratory biomedical scientists who were blinded to the trial arm did the analyses. Wounds were irrigated with warm normal saline before swabbing,[19] and for dry wounds, swab tips were moistened in warm sterile saline.[20] The swab was zigzagged across the whole wound under gentle pressure while being rotated between the fingers,[21] and was immediately stored in transport medium and dispatched to the laboratory as soon as possible. All nurses on the ward and preoperative clinic were educated before the trial on how to swab the wounds.

Definition of infection

Wound infection was defined as a positive swab associated with pain at the wound site, increased exudate, odour, swelling, heat, or local redness. Colonisation was defined as a positive wound swab with no clinical indication of infection.

Outcomes

Primary and secondary outcomes were defined in the study protocol. Primary outcomes were positive wound swabs with or without MRSA at any time up to 28 days after operation. Positive results were reported irrespective of whether or not the wound was infected. Secondary outcomes included duration of hospital stay after operation; sites of infection; positive swab results at 7 days; adverse events including a local reaction in and around the wound; and aspects of feasibility such as recruitment and retention of patients, acceptability of the use of honey to patients and nursing staff (using purposively designed satisfaction questionnaires), completeness of data, and appropriateness of the timing of swabs and the sites from which they were taken.

Statistical method

Main comparative analyses were by intention to treat. Fisher's exact test was used to compare primary outcomes, with 95% confidence intervals (CI) computed for the difference between groups. A 95% CI was computed for the difference in mean duration of hospital stay. Feasibility analyses used descriptive methods. The Mann–Whitney test compared groups in regard to duration of stay, and patients were asked questions with Likert-type responses. Statistical analyses also included power calculations for further study.

The study was approved by Sefton Research Committee in July 2007 and by the University of Salford Research Governance and Ethics Committee in November 2007.

Table 1
Baseline demographics and clinical characteristics of patients.

	Honey ($n = 25$)	Control ($n = 24$)
	No (%)	No (%)
Male	16 (64)	17 (71)
Age 65+	8 (32)	13 (54)
Age 75+	3 (12)	6 (25)
Never smoked	6/22 (27)	7/22 (32)
Ex-smoker	6/22 (27)	11/22 (50)
Current smoker	10/22 (45)	4/22 (18)
Primary treatment	22 (88)	19 (79)
Recurrence	3 (12)	4 (17)
Further disease	0	1 (4)
Osteoradionecrosis	0	0
Clinical stage T3-4	12/24 (50)	12/23 (52)
Clinical N+	5/24 (21)	3/23 (13)
Oral tumour	20 (80)	16 (67)
Oropharyngeal tumour	2 (8)	4 (17)
Other	3 (12)	4 (17)
Soft free-flap	14 (56)	14 (58)
Composite free-flap	11 (44)	10 (42)
Radial flap	14 (56)	12 (50)
Anterolateral thigh flap	4 (16)	3 (13)
Latissimus dorsi flap	0	1 (4)
Fibula flap	1 (4)	4 (17)
Deep circumflex iliac artery flap	5 (20)	2 (8)
Scapula flap	2 (8)	3 (13)
Other	3 (12)	0
Bilateral neck wound	7 (28)	4/23 (17)
Right neck wound	8 (32)	10/23 (43)
Left neck wound	10 (40)	9/23 (39)
Tracheostomy	23 (92)	23 (96)
Full thickness graft	3 (12)	2 (8)
Split skin graft	11 (44)	8 (33)
PEG	4/24 (17)	0
Passive drains	0	0/24
Vacuum drains	25 (100)	23/23 (100)
Previous radiotherapy	2 (8)	4 (17)

Results

Of 70 eligible patients, 56 (80%) agreed to be randomised, and 49 (70%) were actually randomised (Fig. 1) into two groups. Honey dressings were used in 25 and conventional dressings in 24 (controls). Six patients were missed when consent was required, 8 did not consent, and 7 who had consented were missed for randomisation in theatre. Through an administrative error one patient who was randomised to have a honey dressing was actually given conventional treatment, and had negative swab results during follow-up. Analysis of the main intention to treat compared the two groups. Imbalances between the groups were consistent with small sample sizes, notably in age and whether participants smoked or had ever smoked (Table 1).

Positive results were found in 36% of the honey group and 38% of the control group (Table 2), and MRSA was found in 28% and 25%, respectively. The wide confidence intervals for the effect of treatment with honey reflect the sample size. Overall 37% (18/49) of swabs were positive and 27% (13/49) were infected by MRSA. Using 40% and 30% as underlying

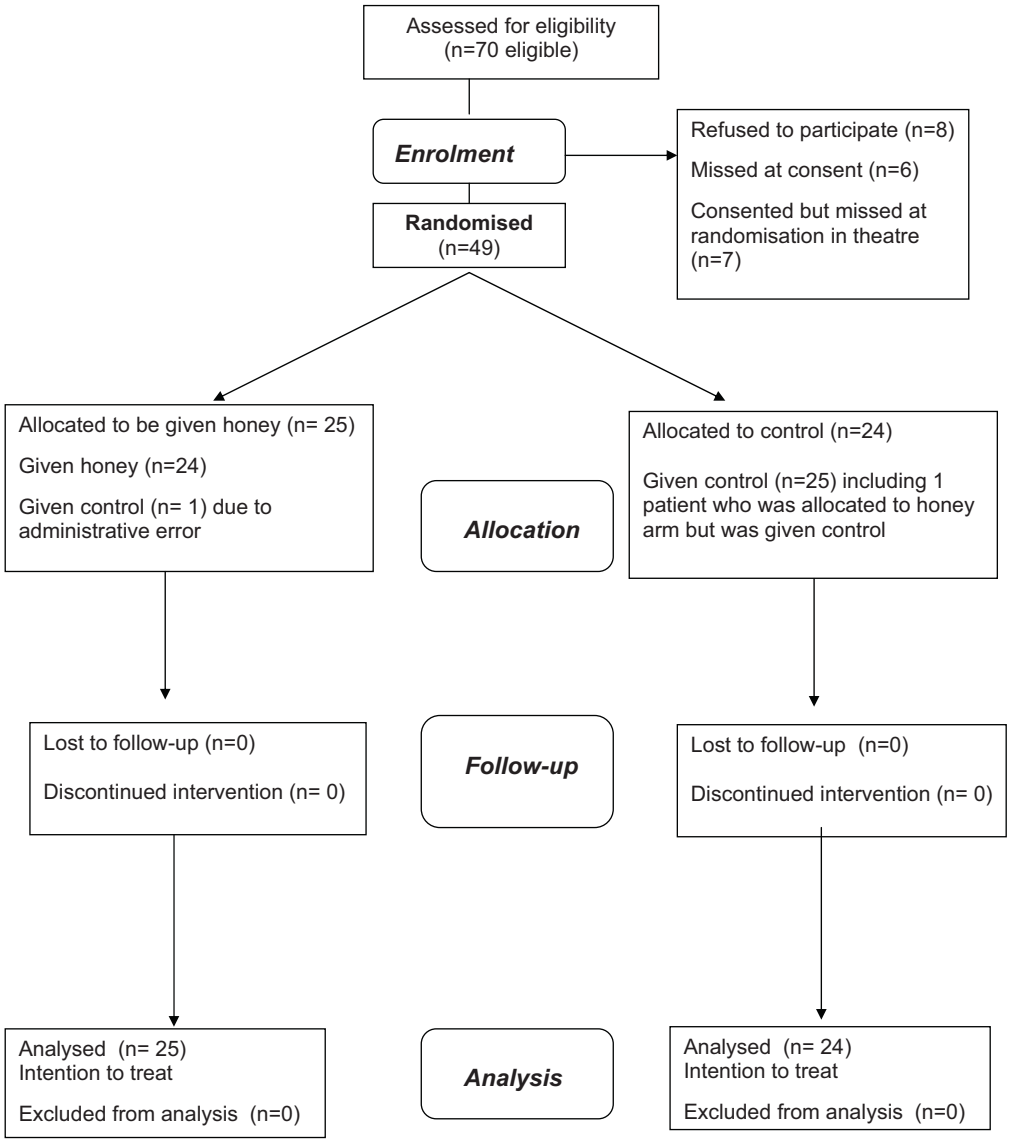

Fig. 1. Flowchart showing enrolment, allocation, and follow-up of patients.

rates, projections of sample size for a more definitive trial are shown in Table 3.

Positive wound swabs were either infected (2/9 honey, 5/9 control) or colonised. The sites of infection in seven patients are shown in Table 4. MRSA was found in swabs from 1/7 honey and 4/6 control patients. Infected swabs with no MRSA were found in 1/2 of the honey group and 1/3 controls. The non-MRSA patients included one with a MSSA infection. Systemic antibiotics were given to all patients with infections.

At 7 days there were positive wound swabs for 20% (5/25) of the honey group, and 13% (3/24) of the control group ($p = 0.70$). No adverse events were reported. Patients in the honey group stayed in hospital for a significantly shorter time after operation than the controls (Table 5). The 95% CI for

Table 2
Primary outcomes, as measured during admission, after admission, and up to discharge or 28 days from operation if still in hospital.

	Honey ($n = 25$) no (%)	Control ($n = 24$) no (%)	P value*
Positive wound swab	9 (36)	9 (38)	>0.90
	95% CI for effect of honey: 29% benefit to 26% detriment		
Positive wound swab for MRSA	7 (28)	6 (25)	>0.90
	95% CI for effect of honey: 22% benefit to 28% detriment		

* Honey compared with control.

Table 3
Calculations of sample size for a randomised trial to detect postulated differences between honey and control arms.

	Difference to be detected (%)	80% power and $p < 0.05$ for analysis by Fisher's exact test no per group	Recruitment numbers after applying a non-participation multiplying factor* no per group
Positive wound swab	40 compared with 35	1511	2159
	40 compared with 30	376	537
	40 compared with 25	165	236
	40 compared with 20	91	130
MRSA wound swab	30 compared with 25	1291	1844
	30 compared with 20	313	447
	30 compared with 15	134	191
	30 compared with 10	72	103

* In this study 70% (49/70) of those eligible participated, and therefore to factor in non-participation of eligible patients to this extent we need to multiply the formal sample size power calculation by 1.43 (100/70) to obtain recruitment numbers.

Table 4
Sites of infection in two patients from the honey group and five control patients.

Group and case No	Sites of infection
Honey	
1	Neck, tracheostomy, hip
2	Arm, split skin graft
Control	
1	Neck
2	Neck, split skin graft
3	Neck, nose, groin
4	Neck, nose, tracheostomy
5	Groin, PEG, tracheostomy, scapula

Table 5
Duration of stay in hospital after operation (days).

	Honey ($n = 25$)	Control ($n = 24$)	P value*
Mean	16	21	
Median	12	18	0.047
IQR	10–21	13–28	
≥28 days	3/25 (12%)	8/24 (33%)	

* Honey compared with control.

the mean difference represents a saving of between 0.2 and 11.2 days.

A patient questionnaire at discharge (or 28 days if in hospital) asked about dressings, wounds, overall care, and experience of being in the trial, and was completed by 84% (21/25) of the honey group and 71% (17/24) of the control group. Responses from the honey group were generally more favourable (Table 6), though not significant. There were very few negative responses and almost all were from the control group: two were dissatisfied about the time it took the wound to heal, and one each was dissatisfied about the comfort of the dressing, the control of odour, the number of times the dressing was changed, and pain for six hours after the dressing was applied. Three from each group said that it was always painful when the dressing was removed.

On completion of the study, 43% (12/28) of nursing staff on the maxillofacial unit completed a questionnaire on their experience in the trial. The first seven questions had five possible responses (very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, very dissatisfied). There were no negative responses and only one middle option response (for overall rating of the dressing). Nurses were very satisfied

Table 6
Number of responses from a survey (10 questions) of trial patients at discharge or at 28 days if still in hospital.

	Summary statistic	Honey group ($n = 21$) no (%)	Non-honey group ($n = 17$) no (%)
1. Overall were you happy with the treatment you received?	Satisfied/very satisfied	20 (95)	15 (88)
2. Length of time it took the wound to heal	Satisfied/very satisfied	18 (86)	11/16 (69)
3. Was the dressing painful after application	10 min or less	17 (81)	10 (59)
4. Was the dressing painful on removal	Always/sometimes	13 (62)	11/16 (69)
5. Comfort of the dressing	Satisfied/very satisfied	18 (86)	13 (76)
6. Control of odour	Satisfied/very satisfied	17 (81)	14 (82)
7. Number of times the dressing had to be changed	Satisfied/very satisfied	19 (90)	14 (82)
8. Written information about the trial	Satisfied/very satisfied	20 (95)	12/16 (75)
9. If it was necessary to contact you again about the trial, would you mind?	Happy to be contacted	19 (90)	15 (88)
10. Did you enjoy being part of the trial?	Yes	20 (95)	15 (88)

Possible responses. For questions 1, 2, 5, 6, 7, and 8: very satisfied; satisfied; neither satisfied nor dissatisfied; dissatisfied; very dissatisfied. For question 3: 10 min or less; 1/2 to 1 h; 2 h; 6 h. For question 4: always; sometimes; never. For question 9: happy to be contacted; do not contact me. For question 10: yes; no. There were no significant differences (even at the 20% level of significance) between groups for questions 1–8 using Mann–Whitney test and the full range of ordinal response, or for questions 9–10 using Fisher's exact test.

with the application of honey ($n = 7$), removal of dressings ($n = 5$), time that dressings were worn ($n = 5$), residue on the skin ($n = 2$), condition of surrounding skin ($n = 4$), overall improvement of the wound ($n = 5$), and overall rating of the dressing ($n = 6$). In response to two other questions, all 12 nurses felt that honey had a valued place in the management of wounds, and all 12 would be prepared to use honey dressings on other patients.

Discussion

To the best of our knowledge this is the first surgical trial to evaluate the possible effectiveness of honey dressings in reducing wound infections. Patients who have free tissue transfer for head and neck cancer are good models with which to carry out an evaluation because around a quarter develop MRSA postoperatively from multiple wound sites.[12] Patients are increasingly involved in their treatment and from the author VR experience some patients tend to favour natural and complementary therapies, so if the theoretical evidence for honey as a dressing is confirmed, they might wish to choose it.

In this feasibility study data completeness was good and the intention was to recruit sufficient numbers to make a critical assessment of the study design and indicate how many patients would be required for a larger multicentre trial. Follow-up was limited in this study and it was not possible to report the time taken for wounds to heal completely, or whether MRSA was eradicated. Although there was a working definition of wound infection, it would be possible to make it more rigorous by the use of the ASEPSIS method of scoring postoperative wounds for infection.[22] This is important for testing clinical efficacy and for addressing the issue of assessor blindness as there is no placebo for honey. The ethical committee refused to allow the inclusion of basic clinical characteristics of patients who declined to take part, which limited our ability to analyse the whole group at the trial centre.

Our patient and staff surveys suggest that honey dressings were tolerated well with minimal pain reported. Dunford and Hanano [23] reported a 50% reduction in reported levels of pain in their study of 40 patients, and it is unusual for any pain associated with changes in dressing to cause patients to withdraw from studies that involve chronic wounds.[15] Honey dressings are inexpensive and compare favourably with the cost of standard dressings used in this trial, roughly £19.05 for standard dressings for 10 days compared with £17.31 for honey.

By virtue of the frequency of swabbing, this study has given a good indication of the incidence of MRSA in patients having free tissue transfer; the rate being around one quarter, of which 38% were categorised as infection rather than colonisation. One of the unexpected findings was a reduction in the duration of hospital stay in patients who had honey dressings. Systematic effects in a small study could explain this, but if it really were reduced, even by two days/patient, it would lessen the costs for 100 free flaps by 200 bed days, which equates to about £30K. Of course, there are many factors that contribute to duration of stay, and further research is required to account for any possible confounding factors – for example, age, social circumstances, or comorbidity.

This study has shown that a randomised trial is feasible in this group, and that a single centre study cannot draw any firm conclusions about the efficacy of honey compared with standard dressings. Confidence intervals are wide, and as anticipated, our results cannot rule out a large and significant benefit or even significant detriment from the use of honey. Several hundreds of patients are needed for a multicentre trial, which although expensive to conduct, would clarify the merit of honey as prophylaxis to reduce rates of wound infections and shorten hospital stay.

Patients having free flaps form a suitable model, and a full RCT is feasible with only minor modification to the trial study design. It might be that honey promotes more rapid healing and helps reduce duration of hospital admission, and if a multicentre trial is prohibitively expensive, it would be beneficial to conduct rigorous audits into its use as a standard postoperative dressing.

Acknowledgements

The lead author completed this work as the basis of a professional doctorate thesis. The PhD supervisors, Stephen Barrow, Dr Janelle Yorke, and Simon Rogers are recognised for their support. We thank Mr Brown, Mr Shaw, and Mr Vaughan for allowing their patients to be included in the study, and thank the honey companies Comvita, Medihoney, and Dermasciences for providing the honey samples.

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